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Patentanmeldung Nr. Patent application No. Demande de brevet n°

03293281.6

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Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
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R C van Dijk

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Anmelder/Applicant(s)/Demandeur(s):

PPG - SIPSY
Z.1. la Croaix-Cadeau,
B.P. 79
49242 Avrillé cedex
FRANCE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

New process for the synthesis of eneamide derivatives

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Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

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NEW PROCESS FOR THE SYNTHESIS OF ENEAMIDE DERIVATIVES.

The present invention relates to a new process for the large-scale preparation of ene-amide derivatives useful as valuable substrates for asymmetric hydrogenation reaction and hence for the synthesis of enantiomerically pure amines derivatives known as key intermediates for active pharmaceuticals.

Several methods have been described in the prior art, for example in WO 99/18065 to prepare ene-amide precursors, but these methods are clearly not very general and unsuitable for large-scale production.

The articles JOC, 1998, 63, p 6084 of the authors M. Burk and Coll. and JOC, 1999, 64(6), p 1775 of the authors X. Zhang and Coll. describe a process for ene-amide compounds synthesis comprising the reduction of oxime derivatives with iron metal in presence of acetic anhydride/acetic acid or acetic anhydride only.

The US4194050 patent describes a process for ene-amide compounds synthesis comprising the reduction of oxime derivatives with ruthenium catalyst in presence of carboxylic anhydride.

However, these processes show some limitations such as product decomposition under these conditions, use of co-solvent to facilitate product isolation, impure ene-amides which required arduous purifications and low to moderate yields.

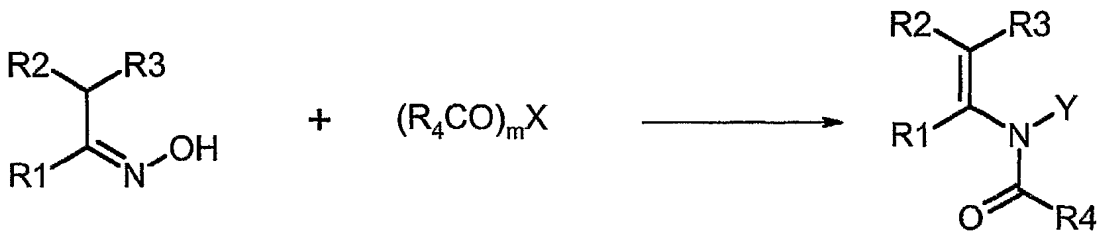
Prior art processes are unsuitable for large-scale production of ene-amide derivatives and hence not applicable to the commercial preparation of chiral amines via asymmetric hydrogenation.

The process according to the invention presents the advantages of obtaining ene-amides in good yields, great facility of product isolation, an excellent chemical purity of product and reproducible process.

The process according to the present invention is clearly suitable for the large-scale industrial production of amine derivatives, via an asymmetric or not hydrogenation reaction. These amine derivatives, asymmetric or not, are used as intermediates for active pharmaceuticals preparation.

The present invention relates to a new process for the preparation of compounds of formula (I), comprising a hydrogenation-isomerization reaction of compound of formula (II) with an acyl derivative of formula (III) in presence of a heterogeneous catalyst as shown in scheme (I).

scheme (I) :



(II) (III) (I)

wherein

R1 and R2 and R3 are independently a hydrogen atom, an alkyl, a cycloalkyl, a cycloalkylalkyl, an alkylaryl, an aryl, a heterocycle, a cyano, an acyl, an alkoxy, an aryloxy,

a carboxyl, a carbamoyl, -CONR5R6 (in which R5 and R6 are independently an alkyl, arylalkyl or aryl group) or

—COOR5 group (in which R5 is an alkyl, alkylaryl or aryl group),

said alkyl, cycloalkyl, cycloalkylalkyl, alkylaryl and aryl groups being substituted or not with a functional group or with R5;

or R1 and R2 taken together, may form a ring (which terms includes mono-, di- and higher polycyclic ring systems);

R3 has the same meanings as R1 or R3 is a hydroxyl, imidazolyl, N-acylimidazolyl, indolyl, N-acylindolyl group or one of the groups, -COR5, -OR5, -OCOR5, -NR5R6, -NHCOR5, $-N(COR5)_2$, wherein R5 and R6 are independently an alkyl, alkylaryl or aryl group;

R4 is a hydrogen atom, an alkyl, an aryl, an alkylaryl, said groups are substituted or not with a halogen atom as Cl, Br, or F;

Y is a hydrogen atom or R4CO group;

X is an oxygen atom or a leaving group and

m is an integer 1 or 2;

when m is 1 then X is a leaving group; when m is 2 then X is a oxygen atom.

As used herein, unless the context otherwise requires:

The term "alkyl" preferably means a straight or branched alkyl group having 1 to 20 carbons atoms such as, but not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl optionally substituted with a functional group or with R5.

The term "cycloalkyl" preferably means a cycloalkyl group having 3 to 20 carbon atoms, such as, but not limited to, cyclopropyl, cyclopentyl, cyclohexyl optionally substituted with a functional group or with R5.

The term "cycloalkylalkyl" preferably means a cycloalkylalkyl group having 3-20 carbon atoms such as but not limited to cyclopropylmethyl, cyclohexylmethyl optionally substituted with a functional group or with R5.

The term "aryl" preferably means an aryl group having 6 to 20 carbon atoms such as but not limited to phenyl, tolyl, xylyl, cumenyl, naphthyl optionally substituted with a functional group or with an alkyl or with a fused aryl, or "aryl" means a heteroaryl group having 6 to 20 carbon atoms such as, but not limited to, furyl, thienyl, pyrrolyl, imidazolyl, pyridyl, pyrazyl, pyrimidinyl, indolyl, carbazolyl, isoxazolyl, isothiazolyl optionally substituted with a functional group or with R5 or with an alkyl or with a fused aryl.

The term "alkylaryl" preferably means an alkylaryl group having 6 to 20 carbon atoms such as, but not limited to, benzyl, phenethyl, naphthylmethyl optionally substituted with a functional group or with R5.

The term "heterocycle" preferably means a heterocycle group having 6 to 20 carbon atoms comprising one more heteroatom as O, N or S such as but not limited pyrrolidinyl, piperazinyl, piperidyl, imidazolidinyl, piperidyl, indolinyl, said heterocycle being saturated or not, said heterocycle being optionally substituted with a functional group or with R5 or a fused aryl group.

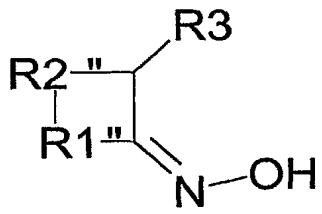
The term "acyl" means preferably —COR5 (wherein R5 is as defined above or such as but not limited acetyl, propionyl, pivaloyl, benzoyl, phenylacetyl). carboxyl, -CONR5R6 in which R5 and R6 are independently an alkyl, alkylaryl or aryl group) or —COOR5 group in which R5 is an alkyl, an alkylaryl or an aryl group,

The term "functional group" means halogen atom, or a group comprising -OH, -OR5, -CN, -COOR5, -COR5, -CONR5R6, -

OCOR5,-NH2, -NHR5, -NR5R6, -NHCOR5 and -N(COR5)2, -NO2, imidazolyl, N-acylimidazolyl, indolyl, N-acylindolyl, -SH, SR5, wherein R5 and R6 are independently an alkyl, an alkylaryl or an aryl group,

The term "leaving group" means preferably one of the groups —COR5, -SO2R5, -COH, -COCCl3, -SO2F, -SO2CF3, -SO2CH2CF3, wherein R5 is an alkyl, an alkylaryl or an aryl group

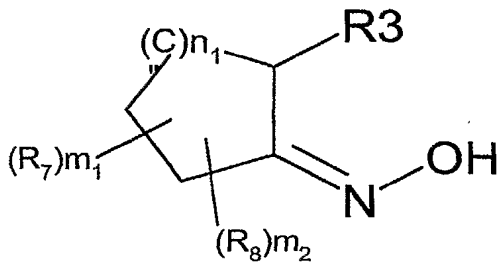
The term "ring" preferably means the formation of ring having 4 to 30 carbon atoms, such as but not limited, compounds of formula hereunder



wherein —R1-R2- is a methylene, dimethylene, trimethylene, tetramethylene, pentamethylene or hexamethylene linkage optionally substituted with a functional group or a fused aryl.

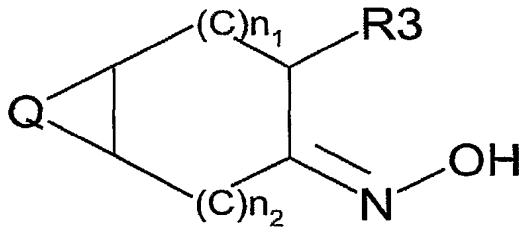
The most preferable compounds are represented by the following formula:

formula (IIA)

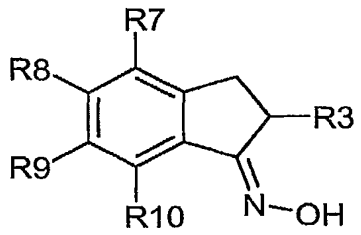


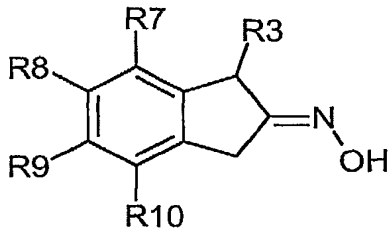
wherein n1 is an integer from 0 to 4, m_1 and m_2 are each an integer from 0 to 4, R7 and R8 different or same, are an hydrogen atom, a functional group, an alkyl, an aryl.

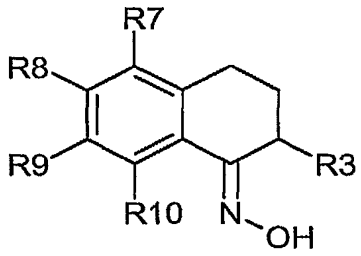
formula (IIB)

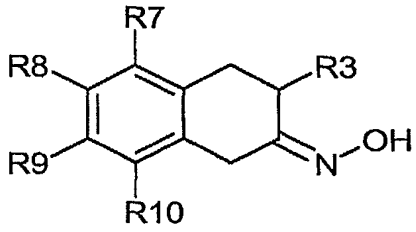


wherein each n1 and n2 is an integer from 0 to 4, Q is an aryl, heteroaryl, cycloaklyl, heterocycloalkyl said group are subtituted or not with at least one functional group preferably alpha- or beta-tretralone-oxime derivatives, alpha- or beta-indanone-oxime derivatives, substituted or not with a functional group.



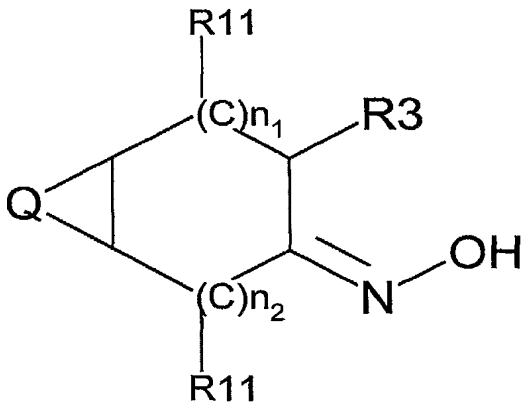






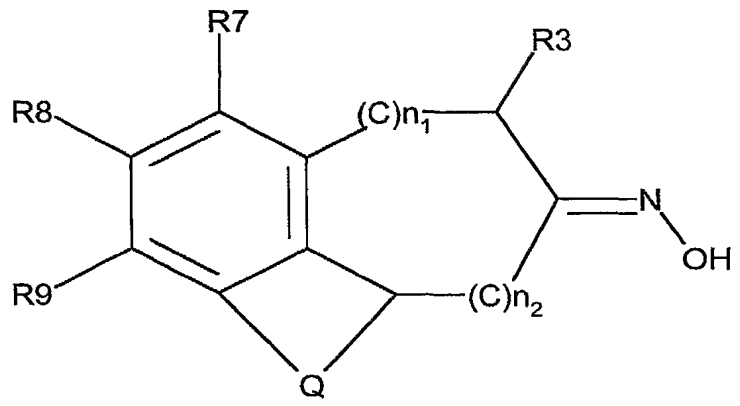
Wherein R3, R7, R8 are as defined above, R9, R10 are independently an hydrogen atom, a functional group, an alkyl, an aryl.

Formula (IIC)



wherein n1, n2, R3 and Q are as defined above, R11 is a hydrogen atom, a functional group, an alkyl, an aryl.

Formula (IID)



wherein n1, n2, R3, R7, R8, R9 and Q are as defined above.

Heterogeneous catalysts are based on metal like Pd, Ir, Pt, Rh, Ni catalysts preferably Ir.

The heterogeneous catalyts is used in the form of an oxide or metallic and may be supported on a suitable carrier (for example Ir/carbon or Ir/alumina).

The method how to carry out the present invention will be explained hereinafter.

The compound of formula (II) may be used as a syn-form, anti-form or a mixed-form of both.

The compound of formula (III) should be used in an amount of at least 2 molar equivalents for one molar equivalent of the oxime and may be used in a large amount as a reacting agent combined with a solvent.

The amount of the catalyst used is in the range of 0.001 to 30% mol, for 1 mol of the oxime derivative.

The process of the present invention is carried out in a suitable solvent. Suitable solvents are aprotic non-basic solvents such as ethers (such as but not limited tetrahydrofuran, tetrahydropyran, diethyl ether, etc.) or aromatic hydrocarbons (such as but not limited to benzene, toluene, etc.) or carboxylic anhydrides or halogenated hydrocarbons or lower carboxylic acids or mixtures thereof.

The process of the present invention is carried out under a temperature range of -20 to 150 °C, preferably between 20 °C to 120 °C.

The hydrogenation of the present invention is carried out under a hydrogen pressure between 0.5 to 20 bars.

The process of the present invention is carried out for a period of time in the range of 0.5 to 24 hours.

The invention will be better understood from the experimental details, which follow.

Examples:

The present invention will be illustrated by the following examples, which will not limit the scope of the invention in any way.

Example 1.

5.5 g (0.0341 mol) of 3,4-dihydro-1H-naphtalene-2-one oxime was dissolved in 42 ml of THF.Then 9.66 ml of acetic anhydride was added dropwise.The reaction mixture is stirred at a temperature between 20-30 °C during 2 hours.

To this reaction mixture is added 0.44 g of the 5% Ir-carbon catalyts.

Then the hydrogenation is carried out at a hydrogen pressure of 6 bars and at 75 °C during 3 hours.

After the catalyst was filtered off, the filtrate was concentrated to dryness under reduced pressure. The residue was dissolved in 120 ml of toluene and concentrated to dryness under reduced pressure.

This new residue was recristallized in a mixture of 10 ml of MTBE and 9 ml of hexane to obtain 3.82 g of the product, the compound N-(3,4-dihydro-naphtalene-2-yl)acetamide

Crude yield: quantitative / Isolated yield: 59.9- %

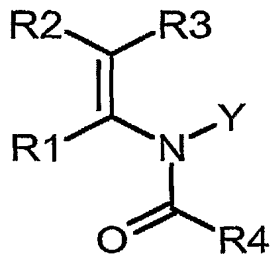
Chemical purity (GC): 98.95 %.

Example 2.

The reaction is carried out in the same manner as in example 1, except that 1-indanone-oxime, methoxy-6- is used as started material. The yield is 83.8 % .The chemical purity is 98.4 %.

CLAIMS

1. A process for the production of ene-amide derivatives represented by the formula (I)



(I)

wherein

R1 and R2 and R3 are independently a hydrogen atom, an alkyl, a cycloalkyl, a cycloalkylalkyl, an alkylaryl, an aryl, a heterocycle, a cyano, an acyl, an alkoxy, an aryloxy, a carboxyl, a carbamoyl, -CONR5R6 (in which R5 and R6 are independently an alkyl, arylalkyl or aryl group) or —COOR5 group (in which R5 is an alkyl, alkylaryl or aryl group),

said alkyl, cycloalkyl, cycloalkylalkyl, alkylaryl and aryl groups being substituted or not with a functional group or with R5;

or R1 and R2 taken together, may form a ring (which terms includes mono-, di- and higher polycyclic ring systems);

R3 has the same meanings as R1 or R3 is a hydroxyl, imidazolyl, N-acylimidazolyl, indolyl, N-acylindolyl group or one of the groups, -COR5, -OR5, -OCOR5, -NR5R6, -NHCOR5, $-N(COR5)_2$, wherein R5 and R6 are independently an alkyl, alkylaryl or aryl group;

R4 is a hydrogen atom, an alkyl, an aryl, an alkylaryl, said groups are substituted or not with a halogen atom as Cl, Br, or F;

Y is a hydrogen atom or R4CO group;

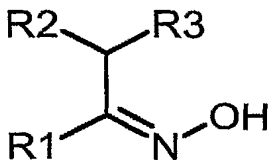
X is an oxygen atom or a leaving group and

m is an integer 1 or 2;

when m is 1 then X is a leaving group; when m is 2 then X is a oxygen atom,

which comprise :

a hydrogenation/isomerization reaction in presence of a heterogeneous catalyst, of an oxime derivatives of formula (II)



(II)

wherein R1, R2 and R3 are as defined above

with an acyl derivative of formula (III)

$(R4CO)_mX$

wherein R4, m and X are as defined above.

2. A process according to claims 1 to 2, wherein the derivative of formula (III) is used in the amount of at least 2 times per mole based on the oxime and may be used in a large amount as a reacting agent combined with a solvent.

3. A process according to claims 1 to 2, wherein the heterogeneous catalyst is based on metal like Pd, Ir, Pt, Rh, Ni catalyst.

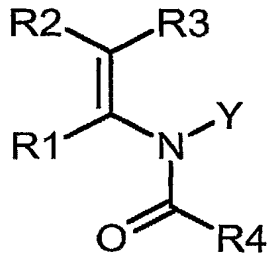
4. A process according to claims 1 and 3, wherein the heterogeneous catalyst is used in the form of an oxide or metallic and may be supported on a suitable carrier and is used in the amount of 0.001 to 30% mole, based on the oxime derivative.

5. A process according to claims 1, which is carried out in a suitable solvent.

6. A process according to claims 1, which is carried out under a hydrogen pressure between 0.5 to 20 bars °C.

7. A process according to claims 1, which is carried out under a temperature range of -20 to 150 °C, preferably between 20 °C to 120 °C.

8. Ene-amide derivative of formula (I)



(I)

wherein

R1 and R2 and R3 are independently a hydrogen atom, an alkyl, a cycloalkyl, a cycloalkylalkyl, an alkylaryl, an aryl, a heterocycle, a cyano, an acyl, an alkoxy, an aryloxy,

a carboxyl, a carbamoyl, -CONR5R6 (in which R5 and R6 are independently an alkyl, arylalkyl or aryl group) or -COOR5 group (in which R5 is an alkyl, alkylaryl or aryl group),

said alkyl, cycloalkyl, cycloalkylalkyl, alkylaryl and aryl groups being substituted or not with a functional group or with R5;

or R1 and R2 taken together, may form a ring (which terms includes mono-, di- and higher polycyclic ring systems);

R3 has the same meanings as R1 or R3 is a hydroxyl, imidazolyl, N-acylimidazolyl, indolyl, N-acylindolyl group or one of the groups, -COR5, -OR5, -OCOR5, -NR5R6, -NHCOR5, $-N(COR5)_2$, wherein R5 and R6 are independently an alkyl, alkylaryl or aryl group;

R4 is a hydrogen atom, an alkyl, an aryl, an alkylaryl, said groups are substituted or not with a halogen atom as Cl, Br, or F;

Y is a hydrogen atom or R4CO group;

X is an oxygen atom or a leaving group and

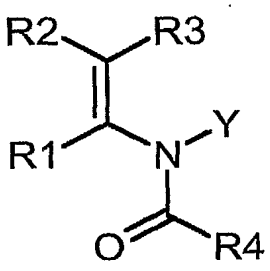
m is an integer 1 or 2;

when m is 1 then X is a leaving group; when m is 2 then X is a oxygen atom,

9. Use of compounds of formula (I) as defined in claim 8 in an hydogenation reaction, asymetric or not, for the obtention of an amine or amide derivative of pharmaceutical interest.

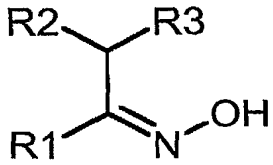
ABREGE

A process for the production of ene-amide derivatives represented by the formula (I)



(I)

wherein R1 and R2 and R3 are independently a hydrogen atom, an alkyl, a cycloalkyl, a cycloalkylalkyl, an alkylaryl, an aryl, a heterocycle, a cyano, an acyl, an alkoxy, an aryloxy, a carboxyl, a carbamoyl, -CONR5R6 (in which R5 and R6 are independently an alkyl, arylalkyl or aryl group) or -COOR5 group (in which R5 is an alkyl, alkylaryl or aryl group), said alkyl, cycloalkyl, cycloalkylalkyl, alkylaryl and aryl groups being substituted or not with a functional group or with R5; or R1 and R2 taken together, may form a ring (which terms includes mono-, di- and higher polycyclic ring systems); R3 has the same meanings as R1 or R3 is a hydroxyl, imidazolyl, N-acylimidazolyl, indolyl, N-acylindolyl group or one of the groups, -COR5, -OR5, -OCOR5, -NR5R6, -NHCOR5, $-N(COR5)_2$, wherein R5 and R6 are independently an alkyl, alkylaryl or aryl group; R4 is a hydrogen atom, an alkyl, an aryl, an alkylaryl, said groups are substituted or not with a halogen atom as Cl, Br, or F; Y is a hydrogen atom or R4CO group; X is an oxygen atom or a leaving group and m is an integer 1 or 2; when m is 1 then X is a leaving group; when m is 2 then X is a oxygen atom, which comprise : a hydrogenation/isomerization reaction in presence of a heterogeneous catalyst, of an oxime derivatives of formula (II)



(II)

wherein R1, R2 and R3 are as defined above with an acyl derivative of formula (III) $(R4CO)_mX$ wherein R4, m and X are as defined above.